REMARKS

Claims 1-13, 15-29, 32-35,and 41-56 are currently pending. The Examiner has maintained the following enablement rejection.

I. Claims 1-13, 15-29,32-35, and 41-56 are rejected under 35 USC § 112, ¶1 as allegedly failing to comply with the enablement requirement.

I. Claims 1-13, 15-29, 32-35, and 41-56 Are Enabled

The Examiner rejects Claims 1-13, 15-29, 32-35, and 41-56 because:

> ... the specification does not correlate to use of any particular saliva specific regulatory element for the creation of transgenic non-human mammals ...

Office Action pg. 2. The Applicant respectfully disagrees. The Examiner maintains this rejection despite the Applicant providing two Declarations demonstrating that: i) a transgenic goat was created using a parotid secretory protein (PSP) promoter (i.e., bSP30a) that secretes an exogenous protein in saliva[1]; and ii) that the nucleic acid sequences of bSP30a and bSP30b promoters were known at the time of filing of the pending application[2].

A. The bSP30a and bSP30b Promoters Are Enabled

In the last response, the Applicant provided evidence that the nucleic acid sequences of the bSP30a and bSP30b promoters were known to those having ordinary skill in the art via "The Wheeler Declaration". The Examiner has acknowledged this evidence by stating that::

> ... the issue is <u>not the availability</u> of the sequences of BSP30a for the creation of the claimed transgenic mammal rather the issue is whether the BSP30 promoter in any transgenic mammal will effectively produce 0.5 mg/ml of the transgene protein product secreted in the saliva. Applicants; have not provided evidence to such an effect. ...

Office Action, pg 11 – 12 [emphasis added]. Since the Examiner insists that the issue is soley polypeptide expression at the 0.5 mg/ml level, claims that lack this requirement should be enabled. In this regard, Claim 29 and Claim 52 should be allowable.

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[1] The Erickson Declaration
[2] The Wheeler Declaration

B. Transgenic Protein Expression In Goat Is Enabled

The Examiner admits that the Applicant has provided evidence that:

> ... a transgenic doe was birthed that has been shown to be transgenic with transfected gene consisting of the bSP30a promoter and the human serum albumin gene. The declaration shows evidence of secretion of the human serum albumin into the transgenic doe's saliva and the transgene is expressed in the salivary gland as evidenced by Western blot analysis.

Office Action pg 4 bridging pg 5. Enablement is met with the presence of a single example:

> The presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered along with all the other factors. To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims.

MPEP § 2164.02: Working Example. As such, the Applicant believes the presently claimed embodiments are enabled for the expression of any protein from an exogenous transgene driven by a bSP30 promoter in the saliva of a goat. To clarify this embodiment, the Applicant has added new Claims 57 - 62 reciting the expression of polypeptides from a transgenic goat.

C. High Level Protein Expression Regulatory Elements Are Disclosed

The Applicant respectfully requests that the Examiner reconsider the teachings of Samuelson because this reference does not discuss FULL PROMOTER sequences of salivary gland specific genes. Specifically, the "limitations" of PSP promoters discussed within Samuelson are directed towards minigene constructs that lack upstream 5' regulatory elements:

> Smaller Psp transgenes containing varying amounts of 5'-flanking sequence fused to a Psp minigene were also expressed in the salivary gland; however, the level of expression in the parotid gland was only 1% of the endogenous gene levels (56)[3]. ... Analysis of various 5' deletion constructs of the Psp minigene localized the position of critical transcriptional control sequences **for basal expression** in both parotid and SLG to a region between –4.6 kb and –3.1 kb. These results indicate that the **minimal salivary-specific enhancer(s)** are within 5 kb of the gene and that enhancer(s) for high level expression in the parotid are located elsewhere ....

Samuelson, pg 217 [emphasis added]. The Examiner is respectfully requested to consider that the Psp minigenes discussed in Samuleson do not contain the 5' expression enhancers as

[3] Mikkelsen et al., Nucl Acid Res. 20:2249-2255 (1992), and discussed within Applicants' specification.

contemplated in the Applicant's specification. The Applicant's claimed promoter and 5' regulatory elements are not minigene constructs, therefore Samuelson's discussion of minigene construct expression limitations are not relevant. If fact, the Applicant has overcome these problems as discussed in Samuelson by disclosing a salivary gland specific promoter comprising cis acting regulatory elements having metes and bounds of 4.6 kB – 30 kB. The Examiner, however, maintains that:

> ... the specification has failed to provide guidance to a salivary gland-specific cis-acting transcription control region ranging between about 4.6 kB-30kB ...

Office Action pg 4. The Applicant disagrees. Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicant has amended Claims 1, 20, 41, and 52 to clarify that the cis-acting regulatory elements are " 5' " promoter sequences. *See, Applicant's Specification pg 27 ln 16.* This amendment is made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application.

The Applicant argued previously that high-expression regulatory elements residing in an upstream 30 kB region of any salivary-specific promoter are disclosed in, and enabled by, *US Patent No. 6,140,552 To Deboer et al.*, "Production of recombinant polypeptides by bovine species and transgenic methods" (*See, Applicants' Specification pg 75 ln 16,* incorporated by reference). Nonetheless, the Examiner discounts this proper incorporation by reference by explaining:

> Patent '522 teaches the mosaic animal that secretes the transgene [product] is comprised of the designed expression vector 16,8hLZ, wherein the 5' flanking region (including the promoter) of the hLZ gene was removed and replaced with the bovine alpha.S1 casein gene promoter ...

Examiner's Action pg 9. The Examiner is respectfully reminded that the DeBoer's teachings regarding the existence of high-expression regulatory elements in the – 30 kB region of salivary specific promoters is NOT limited to the alpha.S1 casein gene promoter. One having ordinary skill in the art, when reading DeBoer et al., would understand that the existence of high expression regulatory elements in the upstream 5' 30 kB region of a salivary specific promoter has general applicability:

> Such *expression sequences* are chosen to produce tissue-specific or cell type-specific expression of the recombinant or secretory-recombinant DNA. Once a tissue or cell type is chosen for expression, 5' and optional 3' expression regulation sequences are chosen. **Generally**, such expression regulation sequences are derived from genes that are expressed primarily in the tissue or cell type chosen. ... *The amount of distal 5' expression regulation sequence* depends upon the endogenous gene from which the expression regulation sequences are derived. **In general,** however, such sequences comprise 5' flanking regions of approximately 1 kb, more preferably 16 kb and most preferably about 30 kb of 5' flanking sequence. ... The determination of the optimal amount of distal 5' expression regulation sequence used **from any** particular endogenous gene ***is readily determined*** by varying the amount of distal 5' expression regulation sequence to obtain maximal expression. **In general,** the distal 5' expression regulation sequence will not be so large as to extend into an adjacent gene and will not include DNA sequences which adversely effect the level of transgene expression.

DeBoer et al, col 8 pg 54 – col 9 ln 67 [emphasis added]. It is of particular interest that DeBoer et al. clearly states that finding an optimal 5' flanking sequence of a secretory promoter to support maximal expression is within the abilities of one having ordinary skill in the art (see, underlined/bolded/italicized portion). Consequently, DeBoer et al. explicitly teaches that finding high expression 5' regulatory sequences in salivary specific promoters does not represent "undue experimentation" to one having ordinary skill in the art.

The Examiner has apparently misunderstood the Applicant's argument regarding DeBoer's teachings in the previous response. The Applicant would therefore like to clarify that DeBoer et al. was not 'incorporated by reference' to provide promoter nucleic acid sequences. As the Examiner has now admitted, the bSP30 promoter nucleic acid sequences were already known in the art and, therefore, explicit disclosure of these sequences in the present application was not required. DeBoer et al. provides teachings for the existence of high expression regulatory elements in any salivary gland specific promoter (i.e., for example, the bSP30 promoters), that when combined with the known promoter sequences provide enablement for the presently claimed embodiments.

Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicants have amended Claims 20 and 41 to delete the phrase "at the level of at least 0.5 mg/ml" because such an expression level is not essential to the presently claimed embodiments. This amendment is made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application.

The Applicants submit that the Applicants' specification does enable the pending claims. The Examiner is respectfully requested to withdraw the present rejection.

CONCLUSION

The Applicant believes that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that all grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicant encourages the Examiner to call the undersigned collect at 781-828-9870.

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By: _____

Thomas C. Howerton
Registration No. 48,650

MEDLEN & CARROLL, LLP
101 Howard Street, Suite 350
San Francisco, CA 94105
781-828-9870